REMARKS

The Office Action has been carefully reviewed. No claim is allowed. Claims 1-3, 5, 11-44 and 47-53 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

The disclosure has been objected to because of improperly demarcated trademark appearing in the specification. The specification is now amended to refer to GenBank as "GenBank®", thereby obviating part of this objection.

Regarding the part of the objection to hyperlinks and/or other forms of browser-executable code embedded in the specification, this part of the objection is obviated by the amendment to page 18 to disclose merely a URL address. MPEP §608.01 VII states that examples of a hyperlink as a browser-executable code prohibited by 37 C.F.R. §1.57(d) are "a URL placed between these symbols '<>' and http:// followed by a URL address. As amended, the URL address on page 18 is no longer a hyperlink or browser-executable, as http:// is not present and the symbols "<>" are not used. URL's, such as now at page 18, are permissible.

Reconsideration and withdrawal of the objection are therefore respectfully requested.

Claims 1-55 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The examiner holds that the specification only adequately describes polypeptides that allow the anchorage of the β_2-microglobulin molecule to the cell membrane wherein the polypeptide comprises the transmembrane and cytoplasmic domain from the MHC I class heavy chain of HLA-A2 which has the amino acid sequence of SEQ ID NO: 2 or wherein the polypeptide comprises the transmembrane and cytoplasmic domain of the human CD3ζ polypeptide. The examiner continues by stating "Furthermore, the specification does not adequately describe the genus of peptides comprising at least one antigenic peptide comprising a MHC class I epitope, wherein said antigenic peptide is not related to an autoimmune disease and only adequately describes antigenic peptides comprising a MHC class I epitope, wherein the peptide has a defined amino acid sequence in the specification (see for example pages 15-17 that discloses SEQ ID NOS giving the amino acid sequence of known MHC class I epitopes." The examiner takes the position that the specification does not describe with any particularity the identifying structural and/or functional features of the genus of "polypeptides that allow the anchorage of the β2-microglobulin to the cell membrane" and the specification provides no correlation of the structure of these polypeptides with their ability to

provide anchorage of β2-microglobulin to the cell membrane that is sufficient to generate antigen specific CTLs and therefore one of skill in the art would not be able to immediately envision which other polypeptides would have the requisite function. This rejection is respectfully traversed.

Applicants respectfully disagree with the examiner that the specification only adequately describes the very narrow scope of polypeptides that allow the anchorage of the β_2-microglobulin molecule to the cell membrane acknowledged by the examiner. A person having ordinary skill in the art of biochemistry would have no reason to question the assumption that if the transmembrane and cytoplasmic domain from the MHC I class heavy chain of HLA-A2, which has the amino acid sequence of SEQ ID NO:2, can be successfully used in the invention as shown in the Examples, then any other transmembrane polypeptide with a cytoplasmic tail could fill the same function of anchoring the polypeptide to the cell membrane.

In fact, in Example 5, it is also shown that a fusion polypeptide comprising CD40 transmembrane and cytoplasmic portion successfully anchors the polypeptide to the cell membrane. Since polypeptides as different as CD40 and HLA-A2 are shown in the present specification to be capable of exerting the same function of anchoring the polypeptide to the cell membrane, there can be

little doubt that any other transmembrane polypeptide with a cytoplasmic tail could fill the same function.

Although applicants do not agree with the examiner's position on lack of written description, the claims are now amended to limit the scope of the polypeptide that allow anchorage of the β_2-microglobulin to the cell membrane to "…a transmembranal and cytoplasmic region of a polypeptide stretch selected from the group consisting of the human CD3 ζ polypeptide, the MHC I class heavy chain of HLA-A, HLA-B or HLA-C molecule and CD40…"

The examiner alleges that the specification discloses that "antigenic peptides comprising a MHC class I epitope that are not related to an autoimmune disease" include, for example MCH class I epitopes from alpha-fetoprotein or MHC class I epitopes from the HIV envelope protein Tat. The examiner holds that the specification is silent as to what diseases are considered autoimmune diseases and therefore one of skill in the art would not be able to immediately envision or recognize which antigen peptides comprising MHC class I epitopes are not related to autoimmune disease because as envisioned by Skolnick et al., Jones and Tosatto et al., one of skill in the art would not be able to predict whether an antigenic peptide was related to an autoimmune disease given just its amino acid sequence. The examiner further states that one of skill in the art would not be

able to recognize the species encompassed by the genus of antigenic peptides to which the claims are directed because multiple species included in this genus, and more particularly specifically recited in the claims, are in fact related to autoimmune disease. For example, the examiner cites Liu et al. (2007) that allegedly shows that the polypeptide alpha-fetoprotein is expressed in some cases of autoimmune hepatitis and Kim et al. (2005), who, according to the examiner, teach that a peptide from the HIV Tat polypeptide can suppress autoimmune diseases. These peptides are described in the specification as a tumor associated antigen and a pathogen association antigen, respectively. The examiner argues that these examples show that among the peptides described in the specification as "antigenic peptides comprising a MHC class I epitope that are not related to an autoimmune disease", some are "known to be related to autoimmune diseases."

Applicants disagree with the examiner's statement that since "the specification is silent as to what diseases are considered autoimmune diseases [and therefore] one of skill in the art would not be able to immediately envision or recognize which antigen peptides comprising MCH class I epitopes are not related to autoimmune disease", because a person of ordinary skill in the art would know what diseases are considered autoimmune diseases. Nevertheless, for purposes of business

strategy, the term "...is not related to an autoimmune disease" is now amended in the claims to "...is not capable of activating autoreactive cells causing an autoimmune disease", which limits the claim to a better-defined genus. This particular language, although not present explicitly in the present specification, is supported by WO01/91698 (PCT/IL01/00506), claim 17 and page 18, lines 6-9 in the specification, which is incorporated by reference in the present application (see page 11, lines 19-20 of the present specification).

In conclusion, the present claims do indeed comply with the written description requirement and reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-55 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The examiner recites the factors considered *In re Wands* when determining if the disclosure satisfies the enablement rejection. The examiner states "it is noted that the specification has not adequately described DNA vaccines, cellular vaccines or pharmaceutical compositions comprising said polynucleotides for the prevention and treatment of cancer or diseases caused by pathogenic organisms, nor has it adequately described the methods of immunizing mammals to treat or prevent cancer or diseases caused by pathogenic organisms. Notably, the specification only provides evidence that antigen specific CTLs

can be generated with a construct comprising as a MHC class I epitope amino acids 257-264 of chicken ovalbumin and therefore does not provide any evidence that applicant was in possession of using the claimed polynucleotides directed to tumor antigens or pathogenic organism antigens as a DNA vaccination, a cellular vaccination or any pharmaceutical composition for the prevention and treatment of cancer or diseases caused by pathogenic organisms. Notably, one of skill in the art would not consider the ability of a construct to generate antigen specific CTLs as representative of the construct's ability to be a DNA vaccine, a cellular vaccine or any pharmaceutical composition for the prevention and treatment of cancer or diseases caused by pathogenic organisms."

The examiner holds that the specification only provides evidence that antigen specific CTLs can be generated with a construct comprising as an MHC class epitope amino acids 257-264 of chicken ovalbumin and therefore one of skill in the art would be subject to undue and unreasonable experimentation to use the claimed products in methods of preventing and treating diseases. The examiner then concludes "…since the specification provides no working examples wherein the claimed products prevent or treat any diseases and merely provide prophetic examples that only give general guidance as to how to use the claimed product to prevent or treat diseases on pages 23-31, the specification is not deemed

sufficient to enable the claims." The examiner is also of the opinion that "… at the time the instant application was filed, the state of the art indicated that DNA and cellular vaccines for the prevention and treatment of diseases was highly unpredictable in the art." The examiner further alleges that "…it is noted that preventing cancer or infection is intractable, if not impossible…" This rejection is respectfully traversed.

Applicants would like to point out that vaccines have been used for more than a hundred years to prevent diseases. Obviously, the vaccines commonly in use today do not prevent infection of cells, but prevent disease by preventing the infectious agent from multiplying and spreading in the host. Also, the present application does not claim a vaccine for preventing infection, but rather for prevention, inhibition or treatment of a disease.

The examiner has cited 14 different documents, most of which were cited to support the examiner's allegation of "the unpredictability of the art." For example, an experiment in Margalit et al. (the inventors in the present application) is cited, in which cells expressing the low-affinity TRP-$2_{181-188}$ peptide elicited potent CTLs and induced protective anti-melanoma immunity but failed to suppress the growth of pre-established tumors. The examiner however appears to have missed the authors' explanation of this apparent paradox, that the initial

administration of MO5 cells (a spontaneous murine B16 melanoma) in a non-immunostimulatory context may have enhanced the activity of regulatory T cells (Tregs) to a level that prevented later induction of TRP-2-specific CTLs by the transformed antigen presenting cells expressing the polypeptide of the invention. The antigen presenting cells used in the experiment disclosed in the cited Margalit et al. publication, the RMA-S cells, are not true dendritic cells and do not possess all the faculties of dendritic cells such as the capability to down-regulate Tregs. Thus, the failed suppression of tumor growth in this case was the consequence of the specific experimental circumstances and not of an intrinsic feature of the cellular vaccine used.

In another document cited by the examiner, Lollini et al teach that "most current tumor antigens appear to be unsuitable targets for cancer immunoprevention" since most do not have "crucial pathogenic role in tumor growth" and/or are ineffective to stimulate both arms of the immune system. Bodey et al. is cited by the examiner to show that some tumors may evade the immune attack elicited by the vaccine by a natural selection process that leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Applicants would like to draw the examiner's attention to the fact that a method causing

very efficient killing of the tumor cells would leave no time for a natural selection process to take place.

The examiner thus cites failed attempts in the past to argue that the present invention cannot possibly succeed. However, the present invention introduces a new mechanism of presenting the (tumor) specific antigen, which is many times more efficient than the naturally existing mechanism used in all past attempts to produce active specific immunotherapy for cancer. The present specification discloses the advantages of the present invention on page 11, lines 5-12 of the present specification as follows:

> Duration of the functional MHC class I/peptide complex on the cell surface is governed by the affinity of the peptide for the MHC molecule. Dissociation of the peptide from its binding groove in the α heavy chain, results in practically irreversible disruption of the ternary complex formed between the α chain, β_2m and peptide. Both latter components are not anchored to the cell membrane and immediately detach from the cell, while the α chain is later internalized. Stabilization of a particular class I/peptide complex by enabling fast re-association is therefore likely to result in high level of presentation of the antigenic peptide.

Attached hereto from the examiner's consideration is a 1.132 declaration executed by Dr. Gideon Gross to present the results of two experiments recently conducted by the present inventors and published in the *Journal of Immunology*, 2006, 176: 217-224. The first experiment shows that mice challenged with MO5 cells, chicken ovalbumin-transfected variant of the

spontaneous murine B16 melanoma, were successfully treated by immunization with a vaccine of the present invention directed to the antigenic chicken ovalbumin peptide.

The second experiment shows that mice immunized with the presently claimed vaccine and then challenged with MO5 cells are protected from the growth of the MO5 tumors. Here, two antigenic peptides are used that are expressed by the MO5 cells; chicken ovalbumin and TRP-$2_{181-188}$, a native tumor associated antigenic peptide of the MO5 cells. The model system used in the second experiment employed two very different antigenic peptides, ectopically expressed chicken ovalbumin and the native tumor associated antigen TRP-2. Thus, applicants have now provided evidence of a relationship between the structure of the invention and its function, which would permit one skilled in the art to immediately envisage the product claimed for the disclosed process.

The exceptionally high efficiency of antigen presentation in antigen presenting cells expressing the polypeptides of the present invention makes the comparison with cellular vaccines disclosed in the documents cited by the examiner irrelevant since those vaccines are inherently inferior to those of the present invention, especially in view of the new results presented in the attached declaration.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /ACY/
Allen C. Yun
Registration No. 37,971

ACY:pp
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\B\BENA\Gross32\pto\2007-11-29amendment.doc